AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of identifying a subject predisposed to ischemic stroke, the wherein said method including the step of comprises:

determining a rate of release of tissue plasminogen activator in a subject; and

identifying a subject predisposed to ischemic stroke by a reduction in the rate of release of tissue

   plasminogen activator in the subject

identifying a mutation in the subject that reduces the release rate of tissue plasminogen activator.

2. (Currently Amended) [[A]]The method according to claim 1, wherein the ischemic stroke is a lacunar stroke.

3. (Currently Amended) [[A]]The method according to claims 1 or 2claim 130, wherein the mutation is located in the tissue plasminogen activator locus.

4. (Currently Amended) [[A]]The method according to claim 3, wherein the mutation is located in an upstream region of the tissue plasminogen activator locus.

5. (Cancelled)

6. (Currently Amended) A method according to any one of claimsclaim 3 to 5, wherein the mutation is located in both alleles of the tissue plasminogen activator locus.

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7. (Currently Amended) [[A]]The method according to ~~claim 6~~claim 3, wherein the mutation is a cytosine to thymine mutation at position −7351 of the upstream region of the tissue plasminogen locus.

8. (Cancelled)

9. (Currently Amended) [[A]]The method according to ~~any one of claims 1 to 8~~claim 130, wherein the identification of the mutation includes detection of the mutation by ~~hybridisation~~ hybridization of nucleic acid isolated or derived from the subject to a reporter nucleic acid.

10. (Currently Amended) A method of identifying a subject predisposed to small vessel occlusion, ~~the~~wherein said method ~~including the step of~~comprises:

determining a rate of release of tissue plasminogen activator in a subject; and

identifying a ~~mutation in the~~ subject ~~that reduces the~~ predisposed to small vessel occlusion by a

reduction in the rate of release ~~rate~~ of tissue plasminogen activator in the subject.

11. (Currently Amended) [[A]]The method according to claim ~~10~~132, wherein the small vessel occlusion manifests clinically as a disease or condition selected from the group consisting of: lacunar stroke, dementia, ischemic heart disease, ~~(including~~ischemic cardiomyopathy~~)~~, peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic gastropathy, ~~(including~~small and large bowel ischemia~~)~~, diffuse pulmonary embolism, and vascular impotence.

12. (Cancelled)

13. (Currently Amended) [[A]]The method according to ~~any one of claims 10 to 12~~claim 132, wherein the mutation is located in the tissue plasminogen activator locus.

14-16. (Cancelled)

17. (Currently Amended) [[A]]The method according to claim ~~16~~132, wherein the mutation is a cytosine to thymine mutation at position –7351 of the upstream region of the tissue plasminogen locus.

18-34. (Cancelled)

35. (Currently Amended) [[A]]The method according to claim ~~35~~132, wherein the mutation is in both alleles of the tissue plasminogen activator locus.

36-37. (Cancelled)

38. (Currently Amended) [[A]]The method according to ~~any one of claims 30 to 37~~claim 132, wherein the identification of the mutation includes detection of the mutation by ~~hybridisation~~ hybridization of nucleic acid isolated or derived from the subject to a reporter nucleic acid.

39. (Cancelled)

40. (Currently Amended) [[A]]The method according to claim 39133, wherein the disease or condition is aselected from the group consisting of: lacunar stroke, dementia, ischemic heart disease, (including ischemic cardiomyopathy), peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic gastropathy, (including small and large bowel ischemia), diffuse pulmonary embolism, orand vascular impotence.

41-48. (Cancelled)

49. (Currently Amended) A method of treating and/or treating a disease or condition associated with small vessel occlusion in a subject, thewherein said method including the step ofcomprises:

administering to the subject a therapeutically effective amount of an agent that increases the rate of

release of tissue plasminogen activator in the subject.

50. (Currently Amended) [[A]]The method according to claim 49, wherein the disease or condition is selected from the group consisting of: a lacunar stroke, dementia, ischemic heart disease, (including ischemic cardiomyopathy), peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic

gastropathy, (including small and large bowel ischemia), diffuse pulmonary embolism, orand vascular impotence.

51-114. (Cancelled)

115. (Currently Amended) An isolated nucleic acid withcomprising:

(i) one or more base substitutions in the sequence according to SEQ ID No.NO: 3, or

(ii) SEQ ID NO:4, or

(iii) a RNA equivalent of (i) or (ii); or

(iv) SEQ ID NO:3 having one or more nucleotide substitutions

(v) SEQ ID NO:4 having one or more nucleotide substitutions;

wherein the isolated nucleic acid hassequences having one or more nucleotide substitutions

are at least 80% homologyhomologous to SEQ. ID No.NO:3 or SEQ ID NO:4, or

wherein the isolated nucleic acid having one or more nucleotide substitutions hybridizes

with the complement of SEQ ID NO:3 or SEQ ID NO:4 under stringent

hybridization conditions comprising hybridization at 6xSSC at 42 °C and washing in

2xSSC at 20 °Cor RNA equivalent thereof.

116-129. (Cancelled)

130. (New) The method according to claim 1, wherein said method further comprises:

determining a reduced rate of release of tissue plasminogen activator in the subject by identifying a

mutation in the subject that reduces the rate of release of tissue plasminogen activator in the

subject.

131. (New) The method according to claim 1, wherein the method is used to (i) identify a subject

suitable for intervention to prevent and/or treat ischemic stroke; and/or (ii) determine the risk of

ischemic stroke occurring in a subject.

132. (New) The method according to claim 10, wherein said method further comprises:

determining a reduced rate of release of tissue plasminogen activator in the subject by identifying a

mutation in the subject that reduces the rate of release of tissue plasminogen activator in the

subject.

133. (New) The method according to claim 10, wherein the subject having a reduced rate of release of

tissue plasminogen activator is suitable for (i) intervention to prevent and/or treat ischemic stroke;

and/or (ii) intervention to prevent and/or treat a small vessel occlusion; and/or (iii) intervention to

prevent and/or treat a disease or condition associated with small vessel occlusion.

134. (New) The method according to claim 49, wherein the agent is monosodium [2-(6-

hydroxynaphthalen-2-yl)-6-methyl-pyrimidin-4-yloxy]acetate dihydrate (JTV-926) or other bradykinin

agonist.